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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,477	SEMPLE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 14-19* is/are pending in the application.

4a) Of the above claim(s) *4 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-12,14 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The specification has been amended, Claims 1, 5, 14 have been amended, claims 20, 21 have been canceled by the amendment dated June 22, 2004.

In view of applicant's amendment to the claims, and in view of applicant's cancellation claims 2 and 13, and further in view of applicant's response on pages 7-9 of the response, the invention directed to "a non-sequence specific immunostimulatory sequence" and CpG containing oligo will be examined the examiner. Thus, claims 4 and 15 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention The examiner further notes that applicant's response while being found persuasive with respect to the "a non-sequence specific immunostimulatory sequence", which has a proper antecedent basis, is not applicable to the "a non-sequence specific immunostimulatory polymer".

Claims 1, 3, 5-12, 14, 16-19, to which the following grounds of rejection are applicable, are pending for examination.

In view of applicant's amendment to the claims, and in view of the withdrawal of the restriction requirement on basis of applicant's currently amended claims, the followings are new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-12, and 16-19 are readable on a genus of non-sequence specific immunostimulatory sequences", when read in light of the as-filed specification (page 6), clearly exclude known sequences which are complementary to a sequence of the genomic DNA of a patient/subject intended for the treatment, wherein the patient/subject can be reasonably construed as to embrace mammals such as farm animals and human patients. These non-sequence specific immunostimulatory sequences according to the disclosure of the specification must be able to provide immunostiumulation through a mechanism which does not depend on a complementary bas-pairing interaction with nucleic acids of a mammal intended for treatment. As such, these claims are claimed generically, and thus, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification only provides sufficient written description of CpG motif containing oligonucleotides and palidromic sequence containing oligonucleotides, which can be claimed generically as such and without having to recite a specific SEQ ID NO:. However, the claims are broadly drawn to other non-sequence specific immunostimulatory sequences, which neither contains CpG motif(s) or padrinomic sequences. Given the fact that the application clearly exclude a sequence structure which is complentary or antisense to any sequence contained in any genome of an enormous number of mammals or subjects, which representative number of species of

genomes are not even readily available at the time the invention was made, it is apparent that the claimed as written clearly embraces claimed emobodiments which are yet to be described at the time the invention was made. Thus, it is apparent that the main thrust of the presently pending claimed invention, which meets the written description requirement, is a genus of CpG motif containing oligonucleotides" or padrinomic sequences" which can be constructed in a form of an oligo, wherein the motifs and/or padrinomic sequences mainly contribute to an elicitation of an immune response when employed in a lipid encapsulated form.

In view of the reasons set forth in the preceding paragraphs, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified sequence that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to "non-sequence specific immunostimulatory sequence(s)" with no chemical structure as claimed in the presently pending claims because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other material(s)

of agents other than those known in the prior art, as admitted by the as-filed specification, having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of non-sequence specific immunostimulatory sequence(s), which must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of a representative number of species of non-sequence specific immunostimulatory sequence(s), which are clearly claimed generically, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1, 5-12, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

An immunostimulatory composition comprising an oligodeoxynucleotide fully encapsulated in a lipid particle comprising a cationic lipid, wherein said oligodeoxynucleotide includes at least one CpG motif or a padrinomic sequence.

Specifically, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention so that it would operate as intended, *e.g.* functions as an immunostimulatory sequence when encapsulated within a cationic lipid based lipid particle.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5-8, 11, 14, 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg. (US Pat No. 6,207,646) or Krieg (US 6,429,199), taken with any of Wheeler (US Pat No. 5,981,501), Maclachlan (WO 99/39741), or Semple (WO 98/51278, wherein inventors other than applicants of this instant application constitute as "another").

The essential feature of the presently pending claims is that a cationic lipid based lipid particle is used to encapsulate a CpG containing oligo so as to construct a fully encapsulated oligo according to the definition by the as-filed specification.

The specification defines the "fully encapsulated" (page 16) as "the nucleic acid in the particles is not significantly degraded after exposure to serum or a nuclease assay that would significantly degrade free DNA. In a fully encapsulatd system, preferably less than 25% of particle nuclei acid is degradedin a treatment that would normally degrade 100% of free nucleic acid...". The specification further define the lipid particles as particles with mean diameter 50-200 nm (page 16).

Krieg *et al.* teach that cationic lipid carriers (column 12, lines 25-34) can be employed in combination with a CpG motif containing nucleic acid polymer as

immunostimulatory nucleic acid complex and with a drug antigen when employed for induction of an immune response to a target antigen. The '646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64).

Krieg states on column 12:

> An "oligonucleotide delivery complex" shall mean an oligonucleotide associated with (e.g. ionically or covalently bound to; or encapsulated within a targeting means (e.g. a molecule that results in higher affinity binding to target cell (e.g. B-cell and natural killer NK) cell) surfaces and/or increased cellular uptake by target cells). Examples of oligonucleotide delivery complexes include oligonucleotides associated with: a sterol (e.g. cholesterol), a lipid (e.g. a cationic lipid, virosome or liposome), or a target cell specific binding agent (e.g. a ligand recognized by target cell specific receptor). Preferred complexes must be sufficiently stable in vivo to prevent significant uncoupling prior to internalization by the target cell. However, the complex should be cleavable under appropriate conditions within the cell so that the oligonucleotide is released in a functional form.

In addition, Krieg ('199) also teaches a CpG containing oligo that can be encapsulated within a cationic lipid or liposome, and can be used as an immunogenic composition and/or in combination with a chemotherapeutic regime, wherein the CpG motif contributes to its immunogenic stimulatory activities. More specifically, column 4 states:

In one aspect the invention is a method for activating a dendritic cell. The method includes the steps of contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated CpG dinucleotide wherein the nucleic acid is from about 8–80 bases in length in an amount effective to activate a dendritic cell. In one embodiment the dendritic cell is an isolated dendritic cell.

The isolated nucleic acid is one which contains at least one unmethylated CpG dinucleotide and which is from about 8–80 bases in length. In one embodiment the unmethylated CpG dinucleotide has a formula:

$$5'N_1X_1CGX_2N_2 3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1 is adenine, guanine, or thymine; X_2 is cytosine, adenine, or thymine; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In another embodiment the unmethylated CpG dinucleotide has a formula:

$$5'N_1X_1X_2CGX_3X_4N3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1X_2 is selected from the group consisting of TpT, CpT, TpC, and ApT; X_3X_4 is selected from the group consisting of GpT,GpA, ApA and ApT; N is any nucleotide and N_1+N_2 is from about 0 25 nucleotides. In a preferred embodiment N_1 and N_2 of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In an illustrative embodiment the isolated nucleic acid is selected from the group consisting of SEQ ID NOS. 20, 24, and 38 46. In another embodiment the isolated nucleic acid is SEQ ID NO.: 84 or 85.

In yet another embodiment the nucleotide of the isolated nucleic acid has a phosphate backbone modification, such as, for example, a phosphorothioate or phosphorodithioate modification. In one embodiment the phosphate backbone modification occurs at the 5' end of the nucleic acid. Preferably the phosphate backbone modification occurs at the first two internucleotide linkages of the 5' end of the nucleic acid. According to another embodiment the phosphate backbone modification occurs at the 3' end of the nucleic acid. Preferably, the phosphate backbone modification occurs at the last five internucleotide linkages of the 3' end of the nucleic acid.

column 5 states:

The isolated nucleic acid is one which contains at least one unmethylated CpG dinucleotide and which is from about 8 80 bases in length. In one embodiment the unmethylated CpG dinucleotide has a formula:

$$5'N_1X_1CGX_2N_2 3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1 is adenine, guanine, or thymine; X_2 is cytosine, adenine, or thymine; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In another embodiment the unmethylated CpG dinucleotide has a formula:

$$5'NX_1X_2CGX_3X_4N3'$$

wherein at least one nucleotide separates consecutive CpGs; X_1X_2 is selected from the group consisting of TpT, CpT, TpC, and ApT; X_3X_4 is selected from the group consisting of GpT,GpA, ApA and ApT; N is any nucleotide and N_1+N_2 is from about 0–25 nucleotides. In a preferred embodiment N_1 and N_2 of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In an illustrative embodiment the isolated nucleic acid is selected from the group consisting of SEQ ID Nos. 20, 24 and 38–46. In another embodiment the isolated nucleic acid is SEQ ID NO.: 84 or 85.

column 22 states:

For administration in vivo, nucleic acids may be associated with a molecule that results in higher affinity binding to target cell (e.g. dendritic cell) surfaces and/or increased cellular uptake by target cells to form a "nucleic acid delivery complex." Nucleic acids can be ionically, or covalently associated with appropriate molecules using techniques which are well known in the art. A variety of coupling or crosslinking agents can be used, for example protein A, carbodiimide, and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP). Nucleic acids can alternatively be encapsulated in liposomes or virosomes using well-known techniques.

As such, both Krieg(s) do teach that his CpG containing nucleic acid polymer or oligonucleotide can be encapsulated within an oligonucleotide delivery complex, and that the complex includes a cationic lipid-based lipid.

Krieg(s) do not teach that the cationic lipid or liposomes are liposome or lipid particles with mean diameter of 50-200 nm, nor do the Krieg references teach the use of the lipid particles so as to fully encapsulate the DNA, thereby protecting the DNA from degradation in the blood or serum containing environment.

However, at the time the invention was made, the concept of employing cationic lipid based lipid particles with mean diameter of 50-200 nm so as to stabilize and protect DNA from the serum or nuclease digestion is well-known in the prior art.

For example, Wheeler teaches cationic lipid based lipid particles, which fully encapsulate DNA, and are serum stable (entire disclosure, abstract, column 2, column 7, lines 20-27, column 8, first full par., column 10, lines 27-30, column 10, lines 41-56, column 22. Specifically named cationic lipids as those elected species as listed in claim 6 and PEG-lipids are also taught on column 9 through column 10.

Likewise, Maclachlan teaches the make and use of a serum stable plasmid lipid particles for use in cancer gene therapy (entire disclosure), wherein the particles are small particles, which typically have a mean particle size of about 50 to about 200 nm, and preferably, of about 60 to about 130 nm (page 15 through page 16). Specifically named cationic lipids such as DODAP, DODMA and PEG-lipids are also taught on page16-18.

Semple *et al.* also disclose such teaching in WO 98/51278 (entire disclosure) Specifically named cationic lipids such as DODAP, DODMA and PEG-lipids are also taught in Semple on page16-18.

It would have been obvious for one of ordinary skill in the art to employ an fully encapsulated lipid particle in the making of an encapsulated DNA of either one of Krieg(s). One of ordinary skill in the art would have been motivated to employ the lipid particles as disclosed in any of the secondary references because all of the references teach that by fully encapsulating by with the use of a small cationic lipid based lipid particle, the DNA would be serum resistant and degradation resistant. As the result, one of ordinary skill in the art would have expected that the encapsulated oligos are stable, and thus, are expected to exert its immunogenic activity when administered to a subject.

Thus, the claimed invention was *prima facie* obvious.

Claims 1, 3, 5-12, 14, 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg. (US Pat No. 6,207,646) or Krieg (US 6,429,199), taken with any of Wheeler (US Pat No. 5,981,501), Maclachlan (WO 99/39741), Semple (WO 98/51278, wherein inventors other than applicants of this instant application constitute as "another") or Tam (US Pat No. 6,086,913), and further in view of Meers.

The rejection of the base claims over either one of Krieg(s) taken with any of Wheeler, Maclachlan, or Semple *et al.* is applied here as set forth above.

The combined references do not teach explicitly an incorporation of an additive therapeutic agent such as drugs and/or antigens into the lipid particles of the combined cited references.

However, at the time the invention was made, the concept of employing combination therapy such as an additional use of antigen or chemotherapeutic drugs in treating tumors is well-known in the prior art, as evidenced by Kriegs and Machlachlan. In addition, Meers *et al.* teaches on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.,* drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal.

Thus, it would have been obvious for one of ordinary skill in the art to further incorporate a drug or an antigenic molecule within the lipid particles of the combined cited references. One of ordinary skill in the art would have been motivate to incorporate additive agents such as antigenic molecules and/or drugs as a matter of enhancing a combination effect and protective effect of the lipid particles. Thus, an addition of well-recognized immune-stimulating agents including those of protein drugs to the teachings provided by the combined cited references would have been minor modifications so as to provide addictive effects, and thereby, would have been obvious to one skilled in the art at the time the invention was made.

Applicant's response (pages 10-14) and the Semple Declaration have been considered fully by the examiner but are not found persuasive because of the new grounds of rejection. With respect to the Declaration, comments regarding the

Felgnerreference has been considered and is found persuasive. However, comments regarding the Wheeler reference and Meers have been considered (item 5, particularly) are not found persuasive because the Wheeer patent is essentially directed to the same problem as recognized by applicant, *e.g.,* namely claimed subject matters drawn to lipid particles with mean diameter of 50-200 nm thereby rendering the nucleic acid encapsulated therein being resistant to serum or nucleases. While more data has been shown in the declaration so as to demonstrate the improved effect of DODACLDOPE encapsulation as compared to aggregates of lipid complexes, such complexes were not relied upon for the stated rejections as set forth above. See Wheeler (US Pat No. 5,981,501), Maclachlan (WO 99/39741), Semple (WO 98/51278).

To further indicate that the concept of employing cationic lipid based encapsulation of nucleic acid is well-known at the time the invention was made, the following references, in addition to the already cited Wheeler I, Wheeler II, Wheeler III and Bailey, are cited to further demonstrated that it is well recognized within the scientific community that it is conventional in the prior art to encapsulate biologically active molecules including negatively charged DNA by using a cationic liposome:

McEver (US Pat No. 5,605,821, first full paragraph of column 21); Chang (US 2002/0162123, Boulikas (US Pat No. 6,030,956, column 13).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632